REMARKS

As an initial matter, the Examiner is thanked for the courtesy extended to Applicant's undersigned representative on June 24, 2008.

Status of the Claims

Claims 1-28, 32-39, 42-48, 52, 54-64, 69 and 72-101 are pending herein.

Claims 4, 7, 11, 14, 19-22, 24, 25, 32, 33, 58-60, 62, 72-75, 80-85 and 87-89 have been withdrawn.

Claim rejection under 35 USC §103(a)—Singh

Withdrawal of the previous rejection of various claims under 35 USC §103(a) as being unpatentable over Singh et al., *Proc. Natl. Acad. Sci. USA*, 2000, 97:811-816 (Singh) is noted with appreciation.

Claim rejection under 35 USC §103(a)—Singh, Thalhamer, Diwan

Withdrawal of the previous rejection of various claims under 35 USC §103(a) as being unpatentable over Singh and further in view of Thalhamer et al., *Endocrine Regulations*, 2001, 35:143-166 (Thalhamer) as evidenced by Diwan et al., *Journal of Controlled Release*, 2002, 85:247-262 (Diwan) is noted with appreciation.

Claim rejection under 35 USC §102(e)—O'Hagan

Various claims are rejected under 35 USC §102(e) as being anticipated by O'Hagan et al. US 6,884,435 (O'Hagan) as evidenced by Thalhamer. This rejection is traversed.

As indicated in MPEP 2131, for a claim to be anticipated:

> ..."The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim, but this is not an *ipsissimis verbis* test, i.e., identity of terminology is not required. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990)....

Thus, rejections under 35 U.S.C. § 102 are proper only when the claimed subject matter is *identically* described in the prior art.

Independent claim 1 presently requires, *inter alia*, microparticles comprising (a) a biodegradable polymer; (b) a cationic surfactant; and (c) an adsorbed polynucleotide-containing species constituting at least 5 percent of the total weight of the microparticles, wherein the cationic surfactant is present during formation of the microparticles, and wherein no cationic surfactant removal step is conducted subsequent to formation of the microparticles.

Dependent claim 27 further requires that the adsorbed polynucleotide-containing species constitute 10 to 30 percent of the total weight of the microparticles.

Dependent claims 28, 91 and 93 further require that the adsorbed polynucleotide-containing species constitute 10 to 20 percent of the total weight of the microparticles.

These loadings constitute elevated loading levels relative to those previously demonstrated. By increasing polynucleotide-containing species loading levels one can, *inter alia*, reduce the amount of polymer that is administered to an animal (for a given dose of polynucleotide-containing species). See paragraph [0006] of the present specification.

Referring to column 14, lines 8-9, the Office Action alleges that O'Hagan teaches that the "polynucleotide" can constitute 0.1 to 10% of the total weight of the microparticle.

Instead, O'Hagan actually teaches that "macromolecules are added to the microparticles to yield microparticles with adsorbed macromolecules having a weight to weight ratio of from about 0.0001:1 to 0.25:1 macromolecules to microparticles, preferably, 0.001:1 to 0.1, more preferably 0.01 to 0.05." See col. 14, lines 6-10.

As previously noted, this passage pertains generally to "macromolecules," which are defined at col. 5, lines 65 *et seq.* to refer to "without limitation, a pharmaceutical, a polynucleotide, a polypeptide, a hormone, an enzyme, a transcription or translation mediator, an intermediate in a metabolic pathway, an immunomodulator, an antigen, an adjuvant, or combinations thereof."

Moreover, even assuming that all ranges of O'Hagan are applicable in their entirety to the entire range of species embraced by the term "macromolecules," the ranges described are not sufficiently specific to constitute an anticipation under the statute and the case law. In this regard, the standard for anticipation is high:

> When the prior art ***discloses a range which touches *>or< overlaps the claimed range, but no specific examples falling within the claimed range are disclosed***, a case by case determination must be made as to anticipation. In order to anticipate the claims, the claimed subject matter must be disclosed in the reference with "sufficient specificity to

> constitute an anticipation under the statute." What constitutes a "sufficient specificity" is fact dependent. If the claims are directed to a narrow range, >and< the reference teaches a broad range, ** depending on the other facts of the case, it may be reasonable to conclude that the narrow range is not disclosed with "sufficient specificity" to constitute an anticipation of the claims. **>See, e.g., *Atofina v. Great Lakes Chem. Corp*, 441 F.3d 991, 999, 78 USPQ2d 1417, 1423 (Fed. Cir. 2006) wherein the court held that a reference temperature range of 100-500 degrees C did not describe the claimed range of 330-450 degrees C with sufficient specificity to be anticipatory. Further, while there was a slight overlap between the reference's preferred range (150-350 degrees C) and the claimed range, that overlap was not sufficient for anticipation. ***"[T]he disclosure of a range is no more a disclosure of the end points of the range than it is each of the intermediate points."*** *Id.* at 1000, 78 USPQ2d at 1424...

MPEP 2131.03 (emphasis added).

The facts of the present case are analogous to those above, if not more favorable to Applicant. As above, no specific examples falling within the claimed range are disclosed by O'Hagan. Moreover, with respect to the broad range disclosed by O'Hagan (i.e., microparticles with adsorbed macromolecules having a weight to weight ratio of from 0.0001:1 to 0.25:1), the high "macromolecule" concentration is more than three orders of magnitude (2500 times) higher than the low macromolecule concentration (*cf.* the relatively narrow concentration ranges of claims 1, 27, 28, 91 and 93). In this regard, it was held by the Federal Circuit in *Atofina, supra*, that a much narrower disclosure of 100-500 degrees C by a prior art reference did not describe the claimed range of 330-450 degrees C with sufficient specificity to be anticipatory. This was true even though the claimed range was completely embraced by the wide range taught in the reference. Moreover, even a range of 150-350 degrees C by the prior art reference was not sufficient for anticipation of the claimed range of 330-450 degrees C in *Atofina*.

With respect to the narrow range disclosed in O'Hagan (i.e., microparticles with adsorbed macromolecules having a weight to weight ratio of from 0.01 to 0.05), there is clearly no overlap between the ranges of instant claims 27, 28, 91 and 93, and only the lower endpoint of instant claim 1 appears[1] to touch this range. As indicated in *Atofina*, "the disclosure of a range is no more a disclosure of the end points of the range than it is each of the intermediate points." Moreover, it is worth emphasizing that whereas the prior art and claimed ranges in *Atofina* were

[1] Actually, the lower endpoint of claim 1 does not quite touch this range. In particular, microparticles with adsorbed macromolecules having a weight to weight ratio of 0.01:1 to 0.05:1 macromolecules to microparticles correspond to microparticles in which the adsorbed macromolecules constitutes 0.99% [0.01/(1+0.01)] to 4.76% [0.05/(1+0.05)] of the total weight of the microparticles, and this is only if one assumes that no species besides the macromolecules and microparticles contribute to the total weight of the microparticles. Otherwise the percentages will be lower.

based on an "apples-to-apples" comparison (i.e., degrees C vs. degrees C), in the present case the comparison is more of a "fruit-to-apples" comparison, if you will (i.e., macromolecule vs. polynucleotide-containing species).

In the response to Applicant's prior arguments, including various arguments presented above, the Examiner has alleged that "O'Hagan et al. teach that the polynucleotide can constitute 1% to 5% of the total weight of the microparticles (column 14, line 9); the value of 5% is the same as the claimed value, and therefore, O'Hagan et al. anticipate the limitation of the polynucleotide constituting at least 5% as recited in claim 1." The Examiner has also alleged that "O'Hagan et al. teach that the polynucleotide can constitute 0.1% to 10% of the total weight of the microparticles (column 14, lines 8 and 9); the value of 10% is the same as the claimed lower point of the claimed range, and therefore, O'Hagan et al. anticipate the limitation of the polynucleotide constituting 10% to 20% or 10% to 30% of the total weight of the microparticle as claimed in claims 27, 28, 91, and 93."

Based on the foregoing, the Examiner argues as follows: "Therefore, the instant case is not similar to Atofina, because in Atofina, while the prior art disclosed a range touching the claimed range, no specific examples falling within the claimed range were given. In the instant case, the claimed ranges are disclosed with specificity by O'Hagan et al. (specific examples are given), and therefore, O'Hagan et al. anticipates the references."

In this regard, a few points should be reiterated here. First, the portion of O'Hagan referenced by the Examiner refers to *macromolecules*, rather than polynucleotides. Second, the values are not exactly the same as the 5% and 10% values claimed (see, e.g., footnote 1). Moreover, the Examiner has erroneously treated the range endpoints as if they were "specific examples." However, as noted in *Atofina supra* "the disclosure of a range is no more a disclosure of the end points of the range than it is each of the intermediate points." (For this reason, a disclosed range of 150-350 degrees C by a prior art reference was held not to describe a claimed range of 330-450 degrees C in *Atofina*.) As in *Atofina*, in the present case, an allegedly disclosed range of 1% to 5% does not anticipate a claimed range of 5% or more (claim 1), and an allegedly disclosed range of 0.1% to 10% does not anticipate either a claimed range of 10% to 20% (claims 28, 91 and 93) or a claimed range of 10% to 30% (claim 27).

The Examiner refers to *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) in Section I of MPEP 2131.03. However, *Titanium Metals Corp.* pertains to

situations in which an actual specific example (more specifically a specific composition) in the prior art was found to lie within a claimed range. See, also the associated section heading in MPEP 2131.03: "I. A SPECIFIC EXAMPLE IN THE PRIOR ART WHICH IS WITHIN A CLAIMED RANGE ANTICIPATES THE RANGE".

Such case law, however, is not pertinent to the present facts in which the Examiner is arguing that the *endpoint of a range* described in the prior art anticipates a claimed range. The more pertinent case law in this instance is *Atofina, supra,* which is described in the following Section II of MPEP 2131.03 and described under the following section heading: "II. PRIOR ART WHICH TEACHES A RANGE OVERLAPPING OR TOUCHING THE CLAIMED RANGE ANTICIPATES IF THE PRIOR ART RANGE DISCLOSES THE CLAIMED RANGE WITH 'SUFFICIENT SPECIFICITY' ". In this regard, *Atofina* makes clear that the endpoint of a *range* described in the prior art is *not* a "specific example" as alleged by the Examiner. Rather, as indicated above, *Atofina* holds that "the disclosure of a range is no more a disclosure of the end points of the range than it is each of the intermediate points." (For this reason, a disclosed range of 150-350 degrees C by a prior art reference was held not to describe a claimed range of 330-450 degrees C in *Atofina,* even though the 350 degree C endpoint value fell within the claimed range.)

With regard to the actual specific examples of O'Hagan, as previously indicated, Example 7 of O'Hagan describes pCMVgp120 ***DNA loads ranging from 0.84 to 2.36%*** with decreasing loading efficiencies ranging from 88% to 59%. These do not meet the at least 5% loadings claimed. The Office Action urges that "the loading efficiency is not 100% and therefore, in order to achieve a loading of 5%, one would have to use more than 5% input polynucleotide." However, this is not at all clear, as loading efficiency was seen to decrease with increasing target load. Moreover, the present rejection is an *anticipation* rejection and thus pertains to what was actually done in O'Hagan, rather than what might or might not have been obvious in view of O'Hagan.

For at least the preceding reasons, it is respectfully submitted that the claimed amounts of adsorbed polynucleotide-containing species are not disclosed with "sufficient specificity" to constitute an anticipation of the claims.

With respect to cationic detergent, as previously noted, claim 52 sets forth a process in which a w/o/w emulsion is formed that comprises polymer and cationic surfactant, wherein the weight-to-weight surfactant-to-polymer ratio is in the range of from 0.0025:1 to about 0.05:1.

O'Hagan teaches that "a weight to weight detergent to polymer ratio in the range of from about 0.00001:1 to about 0.1:1 will be used, more preferably from about 0.0001:1 to about 0.01:1, more preferably from about 0.001:1 to about 0.01:1, and even more preferably from about 0.005:1 to about 0.01:1." See col. 13, lines 32-37. This passage, however, pertains generally to "detergents," which are defined at col. 5, lines 28-36 to "include surfactants and emulsion stabilizers. Anionic detergents include, but are not limited to, SDS, SLS, sulphated fatty alcohols, and the like. Cationic detergents include, but are not limited to, cetrimide (CTAB), benzalkonium chloride, DDA (dimethyl dioctodecyl ammonium bromide), DOTAP, and the like. Nonionic detergents include, but are not limited to, sorbitan esters, polysorbates, polyoxyethylated glycol monoethers, polyoxyethylated alkyl phenols, poloxamers, and the like."

To the extent that these ranges embrace the ranges of method claim 52, they are not sufficiently specific to constitute anticipation under the statute and the case law. See *Atofina supra.* As above, it should be emphasized that whereas the prior art and claimed ranges in *Atofina* were based on an "apples-to-apples" comparison (i.e., degrees C vs. degrees C), in the present case the comparison is more of a "fruit-to-apples" comparison (i.e., detergents vs. cationic detergent).

With regard to the specific examples in O'Hagan, in Example 2 of O'Hagan, 12.5 ml of a 4% PLG solution (which contains 0.5 g PLG) and a 50 ml of a 0.5% CTAB solution (which contains 0.25 g CTAB) are employed, corresponding to 50% CTAB relative to PLG, or a weight-to-weight surfactant-to-polymer ratio of 0.5:1. These percentages are much greater that the range of cationic surfactant used in claim 52. See also Example 1 of the present specification, wherein 16.6 ml of a 6 % PLG solution (which contains 1 g PLG) and a solution containing 10 mg CTAB are employed, corresponding to 1% CTAB relative to PLG. A repeat procedure employed 4% CTAB relative to PLG.

Note also that the 50% CTAB relative to PLG used in producing the microparticles of O'Hagan is outside even the broadest weight to weight detergent to polymer ratio range described in O'Hagan (i.e., a range of from about 0.00001:1 to about 0.1:1). It is recognized, however, that the microparticles produced by O'Hagan using 50% CTAB relative to PLG are

washed with water by centrifugation four times, which would have reduced the CTAB content. As indicated in Singh *supra* (page 815, right column, third paragraph), washing twice with water by centrifugation results in a CTAB level of 4 micrograms of CTAB per milligram of PLG polymer, or a CTAB concentration of 0.4% relative to PLG. The amount of CTAB in the microparticles of Example 2 of O'Hagan, which were washed four times (rather than two) would be at least as low, given that the same relative amount of CTAB was used to form the microparticles of O'Hagan as was used in Singh.

Unlike O'Hagan, the microparticles in claims 1 and 52 are not washed to remove cationic surfactant subsequent to microparticle formation. This is also true of the microparticles of Examples 1 and 2 in the present specification--consequently, the same amount of detergent used to form the microparticles (1% and 4% CTAB relative to PLG) is also present in the microparticles to which the DNA was adsorbed. In O'Hagan, even though 50% CTAB relative to PLG was used in producing the microparticles, the amount of detergent in the microparticles to which the DNA is adsorbed is far less (not more than 0.4% CTAB relative to PLG, for the reasons discussed above). This amount is also less than the amount of cationic detergent in claims 97-99 and 101.

For at least these reasons, reconsideration and withdrawal of claim rejection under 35 USC §102(e) are requested.

Double Patenting

Claims 1-3, 5, 6, 8-10, 12, 13, 15-18, 23, 26-28, 34-39, 42-48, 52, 54, 55, 61, 69, 76-79 and 90-101 continue to be rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 1-19, 24-26 and 35-40 of O'Hagan. This rejection and its supporting remarks are respectfully traversed.

For example, claim 1 of the present application is directed to microparticles comprising: (a) a biodegradable polymer; (b) a cationic surfactant; and (c) a first polynucleotide-containing species adsorbed on the surface of the microparticles, *wherein the adsorbed first polynucleotide-containing species constitutes at least 5 percent of the total weight of the microparticles, wherein the cationic surfactant is present during formation of the microparticles, and wherein no cationic surfactant removal step is conducted subsequent to formation of the microparticles.*

This claim, for example, the italicized portion thereof, is neither taught nor suggested by the claims of US 6,884,435.

The Examiner has asserted, *inter alia*, that the O'Hagan "specification discloses that the polynucleotide can constitute 5% or 0.1 to 10% of the total weight of the microparticle (column 14, lines 6-10) and that the microparticles comprise 0.1 to 10% or 0.5 to 2% cationic surfactant (column 13, lines 30-37)."

Citing MPEP 804, Applicant had previously noted that, when considering whether the invention defined in a claim of an application would have been an obvious variation of the invention defined in the *claim* of a patent, the patent specification can be used as a dictionary *to learn the meaning of a term* in the patent claim, but that the disclosure of the patent may not be used as *prior art* for purposes of an obviousness-type double patenting rejection.

The Examiner has responded, alleging that the patent specification was used to define the "microparticle characteristics" in order to determine whether the claimed invention is an obvious variation of the invention claimed O'Hagan and further alleging that the Examiner used only those portions of the specification pertaining to the invention claimed in the patent.
As authority, the Examiner provides the following citation from MPEP 804 II B, which pertains to *In re Vogel,* 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970) in which it was held that a certain portion of a the patent specification may be "considered" for an purposes of an obviousness-type double patenting analysis (emphasis added):

> Further, those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. *In re Vogel*....The court in *Vogel* recognized "that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim," but that one can judge whether or not the invention claimed in an application is an obvious variation of ***an embodiment*** disclosed in the patent which provides support for the patent claim. According to the court, one must first "determine how much of the patent disclosure pertains to the invention claimed in the patent" because ***only "[t]his portion of the specification supports the patent claims and may be considered."*** The court pointed out that "this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. 103, since only the disclosure of the invention claimed in the patent may be examined."

In this regard, the *Vogel* Court more fully explained its reasoning as follows [emphasis added]:

> The second analysis question is: Does any claim in the application define merely an obvious variation of an invention disclosed and claimed in the patent? In considering the question, the patent disclosure may not be used as prior art. *In re Boylan*, supra [392 F.2d

> 1017, 55 CCPA 1041 (1968)]; *In re Aldrich*, 398 F.2d 855, 55 CCPA 1431 (1968). This does not mean that the disclosure may not be used at all. As pointed out above, in certain instances it may be used as a dictionary to learn the meaning of terms in a claim. It may also be used as required to answer the second analysis question above. We recognize that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim. A claim is a group of words defining only the boundary of the patent monopoly. It may not describe any physical thing and indeed may encompass physical things not yet dreamed of. How can it be obvious or not obvious to modify a legal boundary? ***The disclosure, however, sets forth at least one tangible embodiment within the claim,*** and it is less difficult and more meaningful to judge whether that thing has been modified in an obvious manner. It must be noted that this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. § 103, since only the disclosure of the invention claimed in the patent may be examined.

Thus, the Court in *Vogel*, examined a "tangible embodiment" within the claim. The Court specifically refused, on the other hand, to consider generic portions of the specification:

> ...We must now determine how much of the patent disclosure pertains to the invention claimed in the patent, which is a process to be performed with pork, to which all the patent claims are limited. The specification begins with certain broad assertions about meat sausages. These assertions do not support the patent claims. The patent claims recite "pork" and "pork" does not read on "meat." To consider these broad assertions would be using the patent as prior art, which it is not....

The present case is analogous. The patent claims recite an adsorbed "antigen comprising a polynucleotide" whereas column 14, lines 6-10 of the specification pointed out by the Examiner pertains to adsorbed "macromolecules". Just as "pork" does not read on "meat" (which is held in *Vogel* to include pork), an "antigen comprising a polynucleotide" does not read on a "macromolecule". To consider the broad assertions regarding macromolecules would be to use the patent as prior art, which it is not.

Similarly, the patent claims recite a "cationic detergent" whereas column 14, lines 6-10 of the specification pointed out by the Examiner pertains to "detergent". As above, to consider the broad assertions regarding detergents in the specification would be to use the patent as prior art, which it is not.

Thus, claim 1 is patentable over the claims of O'Hagan. All other claims depend, directly or indirectly, from claim 1 and are patentable over the claims of O'Hagan for at least the same reasons.

Reconsideration and withdrawal of the outstanding nonstatutory obviousness-type double patenting rejection are requested.

Provisional Double Patenting

Various claims have been provisionally rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over certain claims of copending Application No. 11/113,861. This rejection is a *provisional* rejection. As noted in MPEP 804 I B (emphasis added):

> Occasionally, the Examiner becomes aware of two copending applications...that would raise an issue of double patenting ***if one of the applications became a patent.*** ... The merits of such a provisional rejection ***can*** be addressed by both the applicant and the Examiner without waiting for the first patent to issue.
>
> The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications.
>
> ...
>
> ***If the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection*** and permit the application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent.

Here, the double patenting issue has not yet matured for rational argument (i.e., the copending application has not issued as a patent and the claims may be amended/cancelled in the future). Indeed, at a future time, the provisional double patenting rejection may be the only rejection remaining in the present application, in which case the rejection will be withdrawn in accordance with the provisions of MPEP 804.

Furthermore, Serial No. 11/113,861 is a continuation of Serial No. 09/581,772, which matured as O'Hagan above. Thus the arguments set forth above in connection with O'Hagan are to be considered for the present provisional double patenting rejection as well.

CONCLUSION

Applicant submits that this application is in condition for allowance, early notification of which is earnestly solicited. The Examiner is encouraged to contact the undersigned at (703) 433-0510 to discuss any outstanding issues in this case.

Serial No.: 10/757,708

FEES

The Office is authorized to charge any fees that are due as a result of this Response, and to credit any overpayments, to the undersigned attorney's PTO Deposit Account #50-1047.

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I hereby certify that this document and any document referenced herein is being sent to the United States Patent and Trademark office via Facsimile to: 571-273-8300 on Aug. 6, 2008.

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